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Disease-a-Month

The Anemias

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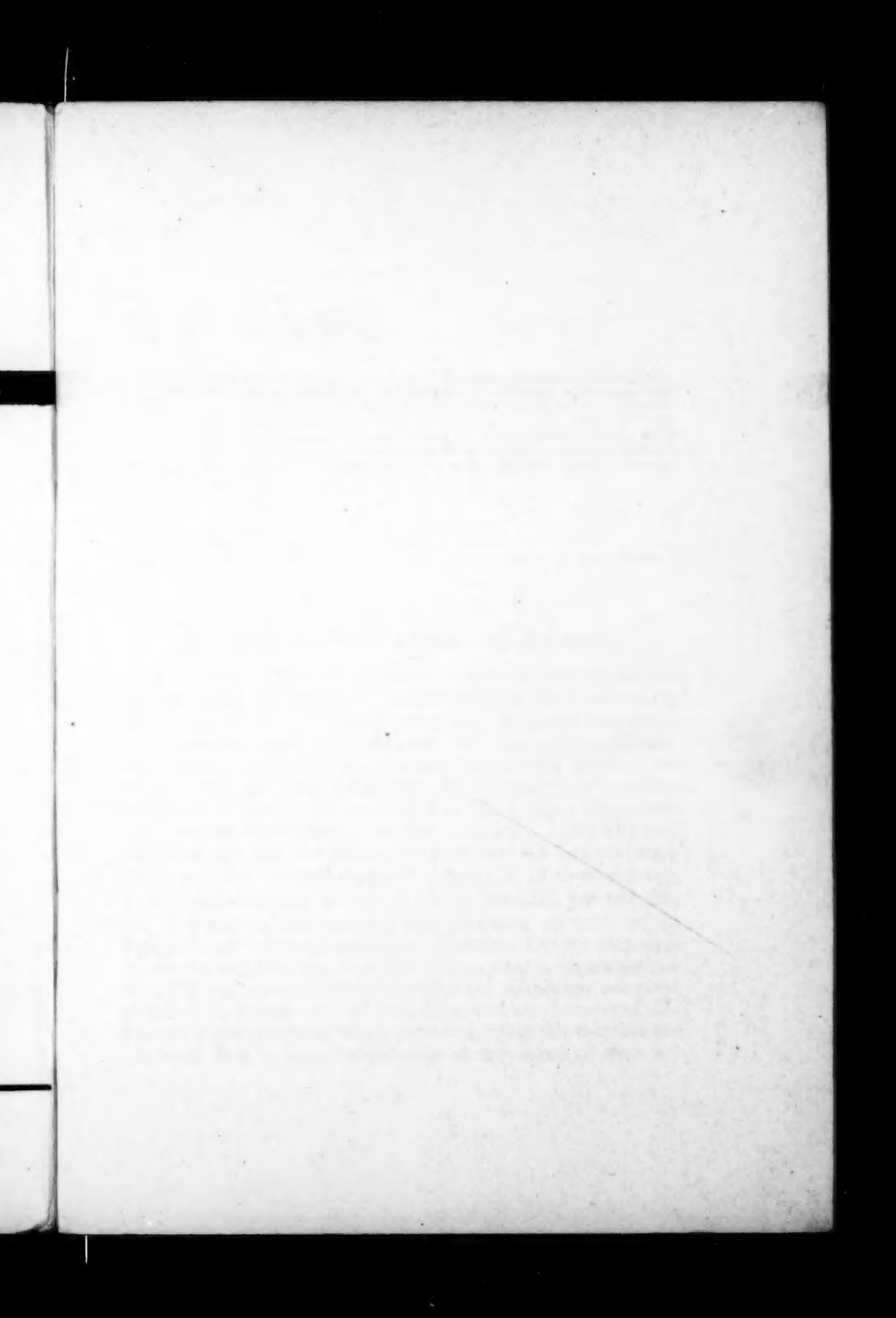*Thomas P. Almy* — CHRONIC AND RECURRENT DIARRHEAS
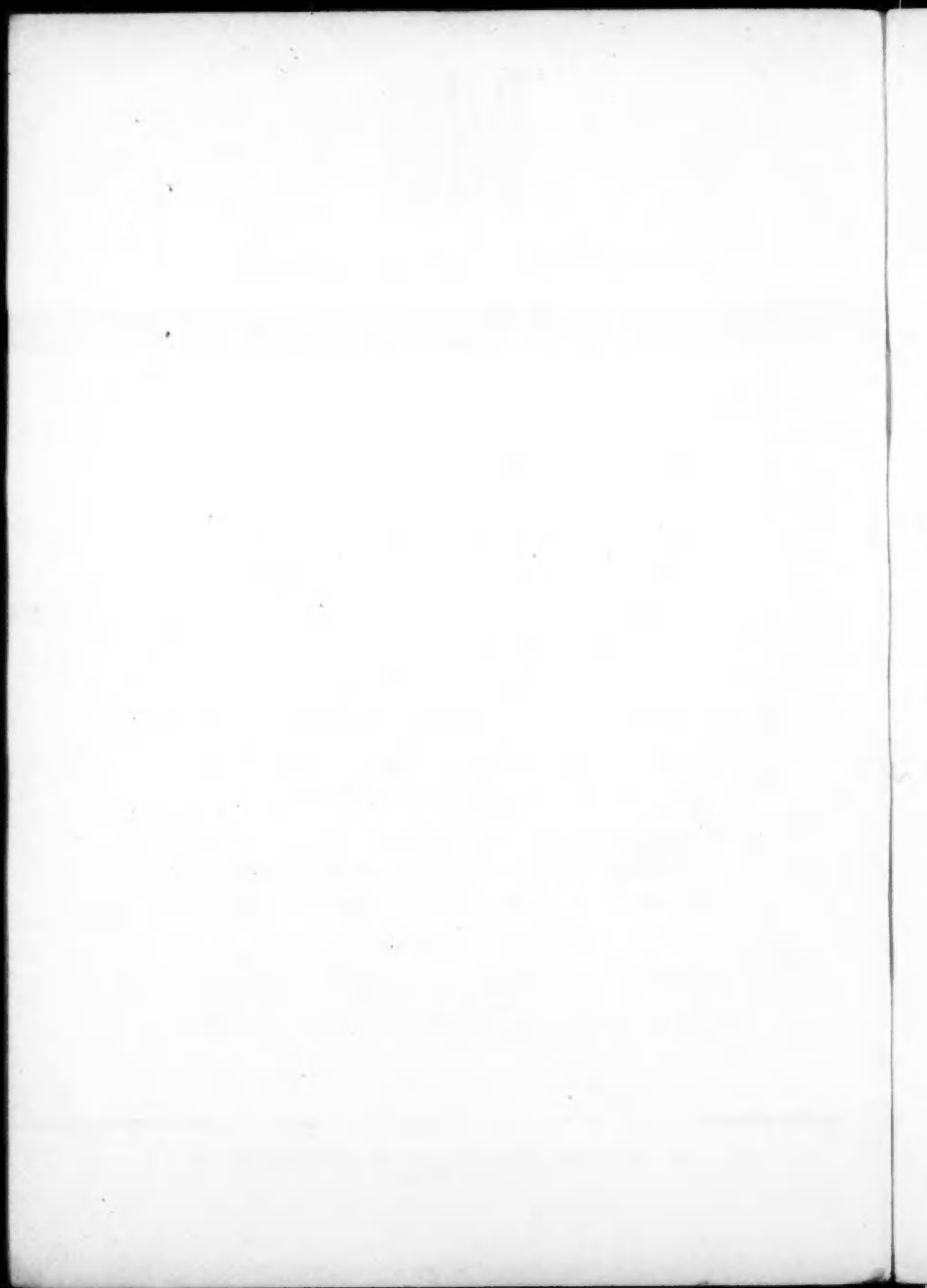
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THE SIGNIFICANCE OF ANEMIA—THE ERYTHRON

THE QUANTITY of red blood corpuscles normally present in
the circulation represents the balance between their production
and their destruction. In a man weighing 70 kg. the circulating
red corpuscles carry approximately 770 Gm. of hemoglobin.
Since there is good evidence that the average "life span" of the
red corpuscles normally is 120 days, the "turnover rate" per day
is the total in the circulation divided by 120. In the average man
this turnover rate amounts to approximately 2.16×10^{11} red
corpuscles per day, or 9 billion per hour, and 6.4 Gm. of hemo-
globin per day. In the process of destruction of these red cor-
puscles approximately 21 mg. of iron is liberated per day, 250
mg. of protoporphyrin and 6.2 Gm. of globin. As indicated in
Figure 1, the iron and globin are reutilized. Of the protopor-
phyrin derived from the destroyed red corpuscles, somewhat less
than 250 mg. appears as fecal urobilinogen since there are great
variations in completeness of evacuation and also because of dif-
ferences in the extent to which pigments giving this reaction are
produced. It is in large measure due to the second of these ex-

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planations that there is such imperfect correlation between pigment excretion and red corpuscle destruction.

The "erythron" refers to the circulating red corpuscles as well as to that part of the hemopoietic system which is concerned with their production and destruction. Under normal conditions there is a fine balance between production and destruction. Increased destruction or the loss of blood normally is met by accelerated production. Through increased production and transformation of yellow marrow to red, the bone marrow is capable of approxi-
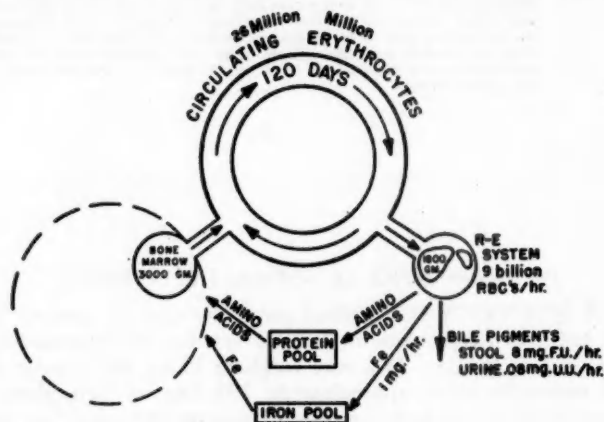

Fig. 1.—The erythron.

mately a seven- or eightfold increase in production capacity (1).

With this picture of the erythron in mind, it follows that anemia will result (1) when there is a lack of materials required for construction of red corpuscles; (2) when there is some defect in the metabolic processes concerned in erythropoiesis; (3) when blood loss or (4) when excessive blood destruction occurs.

ETIOLOGIC CLASSIFICATION AND PATHOGENESIS OF THE ANEMIAS

I. The simplest mechanism whereby anemia develops is through *blood loss*. Anemia due to this cause may be acute or chronic

(Table 1). In the former, the cause of the anemia is usually obvious, although sometimes a large hemorrhage may have occurred under conditions which do not reveal themselves readily. Thus, while hemorrhage in the gastrointestinal tract may be dra-

TABLE 1.—ETIOLOGIC CLASSIFICATION OF ANEMIA

I. Loss of blood
  A. Acute posthemorrhagic anemia
  B. Chronic posthemorrhagic anemia
II. Deficiency of factors concerned in erythropoiesis
  A. Iron deficiency
    Experimentally, also copper and cobalt deficiencies
  B. Deficiency of various B vitamins
    Clinically, B_{12} and folic acid deficiencies (pernicious anemia and related macrocytic, megaloblastic anemias)
    Experimentally, deficiencies of pyridoxine, folic acid, B_{12} and niacin; possibly also of riboflavin, pantothenic acid and thiamine
  C. Protein deficiency
  D. Possibly ascorbic acid deficiency
III. Excessive destruction of red corpuscles, resulting from
  A. Extracorpuscular causes
  B. Intracorpuscular defects, congenital (see IV, A) and acquired
IV. Impaired production of red corpuscles
  A. Congenital or hereditary
    1. Sickle cell anemia and related disorders (hemoglobin C disease, etc.)
    2. Thalassemia
    3. Congenital hemolytic jaundice
  B. Acquired
    1. Anemia associated with infection
    2. Anemia associated with various chronic diseases (renal, etc.)
    3. Anemia in plumbism; following irradiation; in drug sensitivity (aplastic anemia)
    4. Myelophthisic anemias (leukemia, Hodgkin's disease, myelofibrosis, malignancy with metastases, etc.)
    5. Anemia in myxedema and in other endocrine deficiencies

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matic in its symptomatology and may be so severe as to cause shock, it may on the other hand be so insidious that it is not readily recognized.

Chronic loss of blood is a common cause of anemia, yet it is likely to be overlooked. The blood loss may be occult or, even when apparent, it may not be given due attention. This is often

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the case in women, in whom excessive menstrual bleeding may be overlooked as a factor in the development of anemia. In the male, occult loss of blood is practically always from the gastrointestinal tract.

II. The second mechanism whereby anemia may develop, *deficiency of materials essential for red cell construction,* follows naturally in any discussion of the effects of long-continued blood loss. As already indicated, *iron* derived from red cell destruction is reutilized. It has been estimated (51) that the adult male loses or excretes 1 mg. of iron per day, while the adult woman, during the years of menstruation and child bearing may lose, on the average, an additional 0.5–1 mg. per day. If the adult male absorbs an average of 10 per cent of the iron in a diet that contains 12–15 mg. per day, he maintains a positive iron balance rather easily. The adult woman is in a most precarious state, and thus poor diet, poor absorption or excessive menstrual flow or frequently repeated pregnancies may produce a negative iron balance. The demands of growth create a problem for the child who, if birth weight is low, as in a premature infant, and growth rapid, may have his limited supply of hemoglobin diluted more and more in his rapidly expanding blood volume if iron is not provided. The body of a normal newborn infant contains approximately 0.5 Gm. of iron and that of an adult holds 3–5 Gm. There must therefore be a net gain in body iron during the first 20 years of life of 2.5–4.5 Gm., or about 0.35–0.6 mg. per day. As a consequence, the positive iron balance maintained by normal infants and children during their most active growth must be slight and is reversed without too much difficulty.

A long-continued negative iron balance is featured by the development of characteristic changes in the red corpuscles— hypochromic, microcytic anemia. This type of anemia may be encountered in the premature infant, in children and in the adolescent girl even in the absence of blood loss. In the menstruating female blood loss, or the demands of the fetus in the pregnant woman, may be the added burden which trips the scale unfavorably. In the adult male, however, or in the postmenopausal woman who has not reached that state with depleted iron stores, iron deficiency anemia is almost always a signal of chronic blood loss and a warning that the cause must be found.

There is experimental evidence that other metals are also concerned in erythropoiesis. These include *copper* and perhaps even *cobalt*. Experiments in swine (2) have shown that copper is concerned in the absorption and utilization of iron in erythropoiesis. When copper is lacking, a severe anemia develops. This observation, however, appears to have no bearing on clinical practice since the conditions under which copper deficiency is produced are extremely artificial. Copper enters our food in drinking water and through vegetables grown in soils containing copper. The evidence that copper is needed as a therapeutic agent in the treatment of anemias in man is very unconvincing. The role of cobalt in hemopoiesis is obscure.

Among the most exciting of the many studies which have been made in the field of hematology in the past few decades are those which have led to the demonstration of the role of certain of the *B vitamins* in hemopoiesis. In experimental animals it has been shown that most of the B vitamins are concerned in blood formation. *Pyridoxine* deficiency, for example, in swine (3) is associated with the development of severe, microcytic anemia, marked normoblastic hyperplasia of the bone marrow and a profound disturbance in iron metabolism. The last is indicated not only by a high plasma iron content but also by the accumulation of large amounts of iron in the liver, spleen and bone marrow. There is at the same time a striking disturbance in tryptophane metabolism. The administration of pyridoxine corrects these abnormalities promptly and is accompanied by marked reticulocytosis and rapid red cell regeneration.

Deficiency of *folic acid,* experimentally induced (4), is also characterized by severe anemia, in this instance macrocytic in type, and there is also leukopenia and marrow hyperplasia. The changes in the bone marrow resemble those seen in pernicious anemia. When folic acid is furnished, blood regeneration is vigorous and rapid.

In experimental animals, deficiencies of *vitamin B₁₂* (5), *niacin* (6), *riboflavin* and *pantothenic acid* (7) are also accompanied by anemia, although this is less impressive than in pyridoxine or folic acid deficiencies. Thiamine also may be required in hemopoiesis.

Of all of these interesting vitamins, however, only deficiencies

of vitamin B_{12} and folic acid seem to be of any clinical importance. Deficiency of *vitamin B_{12}* is the underlying defect in pernicious anemia and is brought about by failure to absorb this essential nutrient as the consequence of the lack of the gastric "intrinsic factor" (8). In other macrocytic, megaloblastic anemias different mechanisms result in a similar deficiency of vitamin B_{12} or folic acid, or both (see Table 6). Faulty absorption from the small bowel is considered to be the chief cause of the anemia accompanying sprue and idiopathic steatorrhea. The same is occasionally encountered following extensive resection of the small bowel or when there is a gastrocolic fistula. Deficiencies of the remainder of the B vitamins in man are much less severe than those associated with B_{12} and folic acid deficiencies, they are less common and, in some instances, they are actually difficult to produce. Thus, pyridoxine deficiency anemia does not occur naturally in man, and severe anemia has only been produced experimentally on one occasion in a human infant (9). Even with the aid of the pyridoxine antagonist, desoxypyridoxine, only a mild normocytic anemia appeared in a few adult subjects (10).

Protein deficiency without doubt results in anemia in man but, since there exists in the body a "dynamic equilibrium" of the proteins, the deficiency of protein must be very great before hemoglobin production suffers (7). The role of specific amino acids in erythropoiesis in man remains to be worked out.

The role of *ascorbic acid* in relation to anemia has not been established clearly. Anemia accompanies scurvy but it has not been shown to be due directly to lack of vitamin C (8, 11).

It was pointed out earlier that copper deficiency and pyridoxine deficiency anemias have not been observed to occur spontaneously in man even though they are characterized by striking manifestations in experimental animals. This has an important bearing on the relation of experimental studies and clinical practice. Because it has been shown experimentally that certain substances are required for blood formation, it does not necessarily follow that they need to be administered therapeutically to patients with anemia. The reasons for this are several (Table 2). First, the *requirements* for certain substances may be so low that, even in the extraordinary circumstances in which man some-

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times finds himself, anemia attributable to lack of such substances is unlikely or may never occur. Those who assume that such substances must be used therapeutically in man fail to appreciate the fact that the experimental conditions under which certain deficiencies have been produced were extremely artificial.

Storage is another safety factor. The body contains large metabolic pools which can be drawn upon. This explains in part why severe anemia does not develop when there is protein deficiency. It would explain the lack of iron deficiency anemia in a male adult if his diet excluded iron even for 10 years.

It appears likely that *bacterial synthesis* provides us with still another protective factor. Thus, in order to produce folic acid

TABLE 2.—FACTORS GOVERNING DEVELOPMENT OF
NUTRITIONAL DEFICIENCIES

1. *Requirement* for substance in relation to its availability; may vary according to age and condition
2. *Storage* of essential substance
3. *Bacterial synthesis*
4. Factors leading to *conditioned deficiency*

deficiency in swine, we found it necessary not only to give a diet lacking this vitamin but to feed the animals succinylsulfathiazole in order to cut down the growth of bacteria in the bowel (4). In fact, to produce a consistent and severe anemia a folic acid antagonist had to be given.

Finally, as Castle's studies have shown so brilliantly, for the development of certain types of anemia, certain *special conditions* must exist. These he has termed *conditioned deficiencies* (12). The best example of this is the role which lack of "intrinsic factor" plays in the development of vitamin B_{12} deficiency in pernicious anemia. Excessive demands in pregnancy and greater needs for growth in childhood and adolescence may "condition" the development of deficiency and anemia in these circumstances.

III. A third mechanism whereby anemia may develop is through *increased blood destruction (hemolytic anemias)*. As already indicated, the whole red cell mass is replaced approximately every four months. Destruction at a more rapid rate is met by increased production of red corpuscles. Only when de-

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struction exceeds production does anemia develop. Since the bone marrow is capable of approximately a seven-fold increase in activity, anemia is not likely to develop until the "life span" of the red corpuscles has been reduced to less than 15–17 days.

Hemolytic anemia may be due to a large variety of causes. These have been classified as extracorpuscular or intracorpuscular, the latter implying a defect in the red corpuscle itself. By transfusing corpuscles which differ from those of the recipient with respect to their MN or Rh type or by giving group O corpuscles to recipients belonging to one of the other three major blood groups, it has been shown that when normal corpuscles are transfused into patients in whom there is an extracorpuscular cause for hemolysis, the donated corpuscles are destroyed as rapidly as the patients' own cells. If, on the other hand, the patients' corpuscles are removed from their abnormal environment and transfused to a normal recipient, their survival time is normal. In hemolytic anemias due to intracorpusclar defects, the patients' corpuscles, when given to a normal recipient, can be shown to be disposed of more readily than those of the recipient; the latter's corpuscles, if transfused into the patient, maintain a normal "life span."

A classification of hemolytic disorders is presented in Table 3. Hemolytic anemias due to intracorpuscular defects are, in the main, familial and hereditary, in contrast to those produced by extracorpuscular factors, which are usually acquired. The various "intracorpuscular" hemolytic anemias will be considered shortly.

Extracorpuscular causes of increased blood destruction are of great variety and will not be discussed in detail here. Although malaria is the most common cause of hemolytic anemia, when the whole world is considered, this is now a relatively infrequent disease in this country. Other infectious agents which may cause hemolytic anemia include Clostridium welchii, Escherichia coli and other bacteria if septicemia is present. A large number of chemical substances to which man may be exposed occasionally are capable of causing blood destruction (8).

Besides these causes, immune body reactions of various types result in the development of hemolytic anemia (13). Cold hemagglutinins of low titer occur in virtually all normal human serums and are of no pathogenetic significance. They are found

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frequently in high titer in atypical pneumonia, but even there hemolytic anemia occurs only rarely. However, in other circumstances, various types of hemagglutinins and hemolysins play an important role. Immune hemagglutinins in most instances remain attached to the red corpuscle. Immune hemolysins are not found free in the serum except in disorders which require special conditions for their maximum operation. Thus, in paroxysmal cold

TABLE 3.—CLASSIFICATION OF HEMOLYTIC DISORDERS

I. Extracorpuscular causes
   A. Infectious, chemical and physical agents, e.g., malaria, sulfanilamide, severe thermal burns
   B. Vegetable and animal agents, e.g., fava bean, snake venoms
   C. Immune body reactions
      a) Isoagglutinins—transfusion reactions (anti-A, anti-B, etc.)
           —hemolytic disease of newborn (anti-Rh, etc.)
      b) Cold hemolysins—paroxysmal cold hemoglobinuria
      c) Cold, warm and blocking antibodies
   D. Idiopathic "acquired" hemolytic anemia without demonstrable hemolysins or agglutinins
   E. "Symptomatic," e.g., Hodgkin's, chronic lymphocytic leukemia
II. Intracorpuscular defects
   A. Hereditary spherocytosis
   B. Sickle cell anemia and other abnormal hemoglobin syndromes
   C. Paroxysmal nocturnal hemoglobinuria
   D. Thalassemia
   E. Hereditary nonspherocytic hemolytic anemia

hemoglobinuria a fall in temperature is required for maximum activity of the hemolytic system, while in paroxysmal nocturnal hemoglobinuria (PNH) a fall in the pH of the blood is necessary. In the last-named disorder, a normal serum euglobulin, properdin, has been found to be a specific factor in the destruction of the abnormal PNH erythrocyte (14). This requires Mg^{++} and complement for activity and probably produces damage to the cell by combining with the stroma. In certain cases the spleen may be the source of antibodies which coat red corpuscles (15).

One mechanism whereby drugs or chemicals cause hemolysis appears to be by the combination of the drug and a serum factor to produce agglutinating activity. Such a factor has been dem-

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onstrated in the serum of a patient sensitive to Fuadin (16).
Another mechanism has been shown to depend on an erythro-
cytic defect which was found in about 15 per cent of American
Negroes and in occasional Caucasians (17). The presence of this
defect was related to sensitivity to primaquine, sulfanilamide,
acetanilid, phenylhydrazine, thiazolsulfone (Promizole), phen-
acetin and sulfoxone (Diasone). Only old red corpuscles were
sensitive to the drug, and their sensitivity could be demonstrated
by the development of Heinz bodies when they were incubated
with acetylphenylhydrazine. In still other instances the offending
agent acts directly on all the circulating and developing erythro-
cytes and does not require the intermediation of an abnormal
metabolic product in the corpuscles.

Increased susceptibility to mechanical trauma seems to be the
ultimate means whereby cell destruction occurs under normal
circumstances and in many varieties of hemolytic anemia. Nearly
spherical cells, strongly agglutinated cells and those with weak-
ened cell membranes are abnormally susceptible to mechanical
destruction. It has been shown that when red corpuscles are
placed in natural or artificial immune serums in which hemo-
lysins and agglutinins are present, their osmotic and mechanical
fragilities increase. Similar changes in fragility have been ob-
served in association with the action of hemolytic agents such as
saponin or physical factors such as heat. The spleen, in particu-
lar, appears to have the property of selectively removing and
concentrating spheroidal cells (15).

There are many ways in which changes might take place in
the erythrocyte or at its surface and cause increased sensitivity
to mechanical trauma. Enzyme systems which control metabolic
activities essential for the integrity either of the cell as a whole
or of its membranes may fail; there may be loss of metabolic
mobility of some normal constituents of the red corpuscles, such
as cholesterol and phospholipids, which normally are in a state
of dynamic exchange with constituents of the plasma (18); or
the stability of normally stable constituents such as hemoglobin
and stromal protein may be altered. Influences outside the red
corpuscle probably also play a role. Erythrostasis is a term ap-
plied to the processes to which red corpuscles are subjected when
denied free access to fresh plasma. It is possible that tissue lysins

normally inhibited by plasma may be permitted to act under conditions of stasis. This may lead to increased osmotic and mechanical fragility and thereby favor destruction of the red corpuscles.

IV. Although a number of anemias can be attributed to blood loss, impaired production as the consequence of deficiency of essential building stones, or increased blood destruction, as just mentioned, there are many instances of anemia which cannot be classified in this way. It is plausible to consider that a fourth mechanism whereby anemia may develop is through *impairment of the synthetic processes* which normally result in the production of red corpuscles. The fault may be qualitative or quantitative, or both. If it is *quantitative,* fewer than the normal quantity of red corpuscles would be made, but those formed might conceivably be entirely normal or only abnormal to an insignificant degree. If the defect is *qualitative,* abnormal red corpuscles may be produced which are destroyed more rapidly than is usual. As already indicated, increased production may be expected to make up for losses resulting from increased destruction unless the latter exceeds the productive capacity of the hemopoietic system. However, if a quantitative as well as a qualitative metabolic defect exists, the required increased production may not be possible and then anemia will develop. Depending on the nature of the defect in erythropoiesis, the manifestations of the resulting anemia may be expected to be those of impaired production or increased destruction, or both, in different degrees.

Considerable evidence is now accumulating which gives support to this concept. First in this category are several types of anemia which are hereditary in nature and largely hemolytic in their manifestations. These anemias were classified above as *hemolytic anemias due to intracorpuscular defects.* They seem to belong as well in the category now under discussion. Thus, studies of the pathogenesis of sickle cell anemia have revealed that several types of hemoglobin can be distinguished electrophoretically and that, in this disease (19), the production of an abnormal hemoglobin is the fundamental defect. The hemoglobin of sickle cell anemia red corpuscles consists mainly of a component having three more net positive charges per molecule than normal adult hemoglobin in the pH range 5.7–8. In the sickle cell trait, both the abnormal component (hemoglobin S)

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and normal adult hemoglobin (hemoglobin A) are found in the same erythrocytes. As a result of this abnormality, when the corpuscle containing hemoglobin S is deprived of oxygen the sickle

TABLE 4.—INHERITED DISORDERS OF ABNORMAL HEMOGLOBIN

DISORDER	HGB*	HEMOLYTIC ANEMIA	SICK-LING	MICRO-CYTOSIS	HYPO-CHROMIA	TARGET CELLS	SPLENO-MEGALY
None—adult	AA	0	0	0	0	0	0
None—newborn	AF	0	0	0	0	0	0
Sickle cell trait[1]	AS	0	+	0	0	0, +	0
Sickle cell disease[1]	SSF	+++[4]	++	0	0, +	+[5]	0
Hgb C trait[2]	CA	0	0	0	0	++	0
Hgb C disease[2]	CC	+	0	0, +	0	++++	++
Sickle-Hgb C disease[1]	CS	0, +, ++	++	+	±	+++	+
Hgb D trait	DA	0	0	0	0	0	0
Sickle-Hgb D disease[2]	DS	+	+	+	0	0, +	+
Hgb E trait	AE	0	0	0	0	+	0
Hgb E disease	EE	0 ?	0	+	0	+++	+
Thalassemia minor	AA	+[6]	0	+	+	+	+
major	AF	+++	0	++	++	++	+++
Sickle-Thalassemia[2]	SAF	0, +, ++	+	+	++	+++	+
Thalassemia-C disease[1]	CAF	+[6]	0	+	0, +	++	0
Thalassemia-E disease	EF	+++	0	+	+	+	++

*A refers to normal adult hemoglobin; C, D and E to abnormal adult hemoglobin; F to normal fetal hemoglobin; S to sickle cell hemoglobin.
[1] Thus far only in Negroes.
[2] With the exception of one family, thus far only in Negroes.
[3] Sickle cell disease in Caucasians.
[4] RBC survival corresponds as a rule to presence or absence of hemolytic anemia.
[5] Osmotic fragility reduced more or less proportionately to presence or absence of target cells.
[6] Or polycythemia.

shape is assumed. The difference in the surface configuration of S hemoglobin and A hemoglobin enables the former to form more stable aggregates when deoxygenated. Although the cause of the hemolytic manifestations of sickle cell anemia is not entirely clear, it is plausible to consider that conditions producing

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anoxemia and stasis favor sickling and increase the mechanical fragility of the red corpuscles.

This type of investigation has led to other interesting studies. We now know that there exist not only classical sickle cell anemia and sickle cell trait but also related disorders such as hemoglobin C disease (20), sickle-hemoglobin C disease (21) and sickle-hemoglobin D disease (22). Some of the clinical manifestations of these conditions (23) are listed in Table 4. The important observation is that "a molecular abnormality in a simple protein can cause the sequence of events that characterize a single disease" (24).

There is evidence that a similar concept applies to thalassemia (25). Furthermore, the thalassemia trait has been observed to occur in association with the sickling trait and with hemoglobin C, and now also with a new hemoglobin, E (26). It seems likely that several more hemoglobin abnormalities of this type will be discovered.

In the light of these observations, one would postulate (27) that a gene-controlled abnormal synthetic mechanism is also concerned in the pathogenesis of congenital hemolytic jaundice since the defect in that disease has been shown to reside primarily in the red corpuscles. That this is probably the case is indicated by studies which have revealed a disturbance in carbohydrate metabolism in the red corpuscles of congenital hemolytic jaundice (28).

It seems likely that a *disturbance in the production of red corpuscles* not only may be inherited but *can also be acquired.* It is possible that by one means or another the synthetic mechanisms whereby red corpuscles are normally produced become impaired. By interfering with erythropoiesis the metabolic disturbance may result in the production of fewer cells; or defective red corpuscles may be made which are destroyed more readily than is normal. Under this category we have in mind the anemia associated with infection, that associated with various chronic diseases especially renal disease, the anemia in plumbism and following irradiation, perhaps that associated with drug sensitivity (aplastic anemia) and even possibly the anemia seen in association with hypothyroidism and other endocrine deficiencies as well as the whole group of so-called myelophthisic anemias.

In these types of anemia the classical manifestations of hemolytic anemia are unusual. Yet there is evidence that the "life span" of the red corpuscles in many instances is shortened. It seems possible that a metabolic fault in erythropoiesis has led to the production of red corpuscles which are qualitatively somewhat abnormal and, as a result, their life span is shorter than is normal. The absence of classical signs of increased blood destruction can be explained by differences in the rate or perhaps even differences in the manner of destruction as compared with the rate and manner of destruction in the classical types of hemolytic anemia. It is highly probable, furthermore, that in these types of anemia there is also a quantitative defect in the synthetic mechanism so that fewer cells are produced.

It can be freely admitted that the evidence to support this concept of the pathogenesis of these anemias is still only suggestive. What there is may be cited. Thus, it has been observed that infection is associated with a profound disturbance in iron metabolism (29). An increase in free erythrocyte protoporphyrin and in serum copper occurs as well. One finds not only low plasma iron but also reduced plasma iron-binding capacity and decreased incorporation of iron into hemoglobin. The defect cannot be altered by iron administration even if the iron is given parenterally in large quantities. Whether or not the anemia associated with infection is due directly to these changes or is related to them more remotely is unknown. In any event, the profound metabolic defect caused by infection, of which these are presumably some of the manifestations, can be overcome by appropriate treatment of the infection. As this is done, the anemia is also relieved. Various other forms of therapy directed toward relief of anemia, such as the administration of iron, liver extract, vitamin B_{12} or folic acid, are of no value.

The pathogenesis of the anemia associated with chronic renal disease is an enigma. To some degree the anemia is correlated with the retention of nitrogenous waste products (30). In certain instances there is evidence of increased hemolysis (31, 32). In others there is evidence of decreased blood production, while in still others both decreased production and increased hemolysis operate (33). Unlike the anemia associated with infection, hypoferremia is not a constant feature. Like that of infection, how-

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ever, the anemia of renal insufficiency is closely tied with the underlying disease and is uninfluenced by measures other than those which affect renal function. An exception to this statement is the influence of cobalt on both the anemia of renal disease and that associated with infection (34, 35). The nature of this effect is obscure, but it is probably not concerned with the fundamental cause of the anemia.

Inhibition of hemoglobin synthesis through interference in porphyrin metabolism may be a factor in the pathogenesis of the anemia of plumbism (36), but increased hemolysis seems to play a role as well. The anemia which follows exposure to irradiation is probably related to inhibition of nucleic acid synthesis (37). Here too, however, there is some evidence that hemolysis is also a factor. Insofar as the anemia which follows the ingestion of certain drugs is concerned, individual sensitivity and some obscure mechanism leading to bone marrow aplasia seem to be the important factors. These, it appears, have halted the synthetic mechanism.

The pathogenesis of the anemia in myxedema is obscure. Although this anemia disappears gradually as desiccated thyroid is given, it seems unlikely that it is attributable directly to deficiency of the hormone. It has been suggested that it is brought about indirectly through the effect of thyroid hormone on the consumption of oxygen by the tissues (38); when there is thyroid hormone deficiency there is less need for oxygen and fewer red corpuscles are produced. Moderate anemia is also encountered in association with adrenal cortical insufficiency and in cases of hypopituitarism. Although here also the pathogenetic mechanisms are not understood, in view of what is now known concerning the functions of the hormones secreted by the adrenals and the pituitary gland it is at least plausible to ask whether these anemias are but a reflection of the metabolic disturbance resulting from deficiency of these hormones. In these conditions, in order to relieve the anemia it is the endocrine deficiency which must be corrected.

The anemia in leukemia, Hodgkin's disease, malignancy with metastases to bone marrow, myelosclerosis and other similar conditions is often classified as "myelophthisic." There is little or no evidence, however, that the erythropoietic tissue is crowded out

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in these anemias. Their pathogenesis is certainly obscure, but it is noteworthy that the "life span" of the red corpuscles in these conditions may be reduced (39). Here again, it seems plausible that a metabolic abnormality related to the underlying disease is a factor in the pathogenesis of the anemia.

BONE MARROW FAILURE

Anemia, in the last analysis, represents bone marrow failure. If blood is being lost, the presence of anemia indicates the failure of the hemopoietic system to cope with this. In the absence of blood loss, anemia is the consequence of a negative balance between production and destruction. This comes about in a number of different ways. In Figure 2 an attempt has been made to present in graphic form the concept of balance between production and destruction, as well as the fact that the hemopoietic system possesses a reserve capacity for production which, as mentioned earlier, is quite large. The mechanisms involved in the pathogenesis of the anemias which have been just outlined fit well into this kinetic scheme (40).

Quantitative production failure is visualized as being due to the deficiency of a substance essential for erythropoiesis, whether this be one which becomes a part of the red corpuscle or is an accessory in the synthetic process whereby red corpuscles are formed. In this type of disorder, production is reduced and does not keep pace with the normal wear and tear, even though the bone marrow may appear to be "hyperplastic."

There is some evidence that the blood may contain erythropoietic factors ("erythropoietins") which influence red cell formation. For example, an erythropoietic stimulus has been shown to be transmitted from one rat in a low pressure chamber to its parabiotic partner kept at atmospheric pressure (41). The spleen, on the other hand, may exercise an opposing effect. Thus, it has been demonstrated that the spleen remaining in one of a pair of parabiotic rats will prevent the development of the characteristic postsplenectomy leukocytosis (42). It is conceivable, therefore, that quantitative production failure may occur in some instances as a result of lack of erythropoietic stimulation or because of excessive inhibition. Interruption of cell growth or metabolism by

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one of a variety of physical and chemical agents may have a similar effect.

Under *qualitative production failure* may be grouped those types of bone marrow failure in which the fundamental defect is a fault in synthesis, a shunt, so to speak, in the synthetic pro-

RESERVE

PRODUCTION
DESTRUCTION

NORMAL   PRODUCTION
          FAILURE
          (QUANT.)

PRODUCTION
FAILURE
(QUAL.)

SYNTHETIC
DEFECT

SYNTHETIC
DISTURB-
ANCE

EXCESSIVE
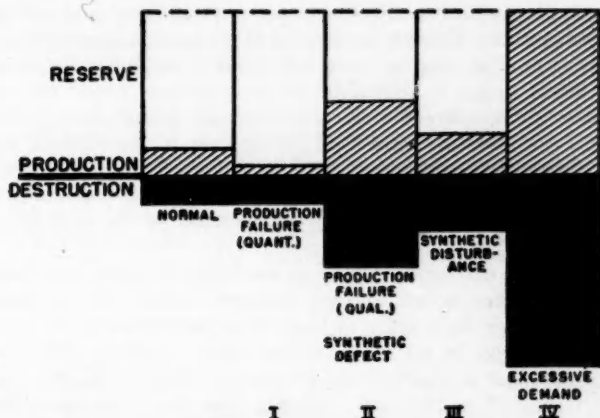DEMAND

I   II   III   IV

Fig. 2.—Bone marrow failure, as represented by an excess of destruction over production. In *I*, quantitative production failure, production is decreased, RBC survival is normal, destruction is normal and the reserve is not utilized. In *II*, qualitative production failure, production is qualitatively abnormal ("synthetic defect"), RBC survival is decreased, destruction is increased and production is accelerated but insufficient. In *III*, "synthetic disturbance," production is impaired quantitatively and perhaps qualitatively, RBC survival is decreased and destruction is increased. In *IV*, "excessive demand," RBC survival is decreased and, if blood destruction is the cause, destruction is increased. Production increases to full reserve capacity but may not be sufficient to meet the demand.

duction line, like that which occurs in sickle cell anemia and in other disorders in which the fundamental defect is in the formation of hemoglobin. The abnormal red corpuscles do not survive the wear and tear of the circulation as well as normal corpuscles. Their "life span" being shortened, blood destruction is increased. The bone marrow is "hyperplastic," it produces more red cor-

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puscles than normally, but this does not keep pace with the increased rate of destruction.

Still another type of production failure is that which is represented by the anemia accompanying many chronic disorders, such as chronic infection and renal disease. It is postulated that the metabolic disturbance which accompanies these conditions causes a quantitative disturbance in erythropoiesis, and also a qualitative one. The qualitative defect is visualized as being responsible for the shortened red cell survival, while the quantitative defect makes it impossible for bone marrow production to increase sufficiently to meet the demand introduced by the shorter corpuscular "life span." In contrast to the "inborn errors" of red cell metabolism resulting from a "synthetic defect" (e.g., in the formation of hemoglobin), in these conditions a "synthetic disturbance" develops as the effect of the underlying disease.

The fourth category of bone marrow failure is easily visualized. The demand for red corpuscles is increased either as the result of increased blood destruction or from blood loss. When production is taxed beyond its reserve capacity, anemia develops. Here no metabolic fault is involved; the problem is purely one of demand and supply. The hemolytic anemias due to extracorpuscular causes fall in this category; those of intracorpuscular origin are considered as falling essentially under the category of qualitative production failure, due to a synthetic defect.

THE RECOGNITION OF ANEMIA—THE MAGIC OF NUMBERS

Since the term anemia refers to a reduction below normal in the quantity of oxygen-carrying material in the blood, the significance of the data obtained in attempting to measure this is of fundamental importance. Anemia is measured by counting the number of red corpuscles, estimating the amount of hemoglobin or determining the volume of packed red cells. Custom and habit have led the majority of physicians to rely on the red cell count for this purpose. Many include also the determination of the hemoglobin level. An increasing number, but as yet the minority, are learning the merits of the hematocrit determination. Relatively few are conscious of the errors to which these various

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measurements are open. Most physicians are inclined to accept at face value the figures which are obtained. This might be called the magic of numbers.

One of the most difficult procedures of all those used in clinical practice is red cell counting. The only person who has faith in a given red cell count is he who has never taken the trouble to repeat it. While such equanimity may have psychological value, it is not very helpful in making a decision concerning the presence or absence of anemia or its degree, or in helping to

TABLE 5.—Errors of Some Routine Hematologic Methods*
(Based on 50 observations)

	S.D.	C.V., %	Significant Difference, $\pm\sqrt{2s^2}$	Probable Minimal Error, %
Red cell count..............	0.415 millions	9.5	1.17 millions	7.8
Hemoglobin	3–5%	3–5	8–14%	2–3
Hematocrit................	0–4%	1.0	1.1%	0.5
MCV (mean corpuscular volume)	10 c.µ	9.6	28 c.µ	7–9
MCHC (mean corpuscular Hgb concentration)	1.6%	5.0	4.5%	2–3

*Compiled from data from Biggs *et al.* (43).
S.D., standard deviation: C.V., coefficient of variation

understand its cause. Similar criticism can be applied to some types of hemoglobin determination. In Table 5 the results of a study of the errors inherent in these procedures are presented (43). This study indicates only the minimal error to which these methods are subject. It does not by any means indicate how great the errors can be in the hands of less well trained or less careful persons.

It is obvious that it is the duty of the physician to select those technical procedures which are likely to be the most reliable. It is most important that his critical judgment should not be blurred by the magic of numbers. One good safeguard is the habit of examining the blood smear oneself. It is as important, or actually more so, for the physician to examine the blood smear as it is for him to look at an electrocardiogram or a roentgenogram, since reports concerning the latter usually come from

physicians expert in these special fields, whereas blood examinations many times are left to poorly supervised technicians of various degrees of training and ability.

DIFFERENTIATION OF THE VARIOUS TYPES OF ANEMIA

THE HISTORY AND PHYSICAL EXAMINATION.—It should be unnecessary to point out that there is no short cut to an adequate history and physical examination. Nevertheless, this cannot be

Chart A.—B.J.B., W F S 16 yr.: "Acute Leukemia"

P.I.: 3 weeks before.—Headache, nausea, weakness.
  Examination revealed pallor (yellowish?), cervical nodes enlarged, splenomegaly. Ht 30, WBC 9400, 71% "stem cells," NRC in smear. Diagnosis: "stem cell leukemia"; B̶ Roncovite.
P.E.: Slight pallor, slight scleral icterus, lymphadenopathy (cervical, axillary, inguinal), liver 1.5 cm., spleen 3 cm., firm, no purpura, rash or sternal tenderness.
Blood: Ht 36; platelets 420,000; WBC 7200, 22% "infect. mono." cells, heterophil antibodies 1:224; also polychromatophilia, stippling, H J bodies, spherocytes and 9.5% reticulocytes.
Serum Bilirubin 2 mg., U U inc., Osmotic Fragility 0.56–0.40 (0.48–0.36 control), Coombs negative.
Family: Father—occasional indigestion only; many previous negative examinations; sclerae slightly icteric, spleen 3 cm., Ht 40, osmotic fragility 0.52–0.40.
  Probably same disorder in his sister and her two children.
Conclusion: Infectious mononucleosis complicating hereditary spherocytosis. A thorough examination corrected a tragic mistake and uncovered a familial disorder.

repeated too frequently for, all too often, a patient has been treated for anemia without a search for its cause or a consideration of its nature; or an "obscure" anemia has been puzzling because the history and examination have not been thorough. The wary physician will not overlook the blood pressure, which may be the clue to the existence of serious renal disease as the cause of the anemia, nor will he fail to look at the sclerae, where a faint tint of jaundice may be perceived, revealing thus the first clue to the possible existence of a hemolytic anemia. He will palpate the bones and particularly the sternum to make certain that there is no tenderness there, and he will not overlook the

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heart because the anemia associated with subacute bacterial endocarditis with its accompanying splenomegaly and petechiae may trip the unwary. It may be pointed out that family histories, as they are ordinarily obtained, are usually misleading. Frequently the historian has little worthwhile information. If a family history is really of interest, actual examination of the members of the family is often necessary (Chart A).

No attempt will be made here to discuss the clinical manifestations of the different types of anemia or their differential diagnosis. These are either well known to the reader or are easily accessible. It will be more profitable to consider a few details from the standpoint of the laboratory.

STUDY OF THE BLOOD—MORPHOLOGIC CLASSIFICATION OF ANEMIA.—Although it is the ultimate purpose in the study of a patient who has anemia to discover its cause and to treat the condition accordingly, before this goal has been reached it is necessary to examine the blood. Consequently, the classification of anemia on morphologic grounds will be found to be a useful step toward the ultimate goal. This is due to the fact that different etiologic factors produce different morphologic types of anemia (8).

On the basis of the mean corpuscular volume (MCV) and the mean corpuscular hemoglobin concentration (MCHC) three or four groups can be distinguished: (1) the macrocytic anemias; (2) the normocytic anemias, and (3) the microcytic anemias. These last anemias include a well defined group, the hypochromic microcytic anemias, and another, referred to as "simple microcytic," because in this type of anemia the reduction in the hemoglobin content of the cells corresponds to the reduction in red cell size, with the result that the MCHC is not significantly reduced.

Macrocytic anemias are characterized by an increase in the average volume (MCV) and weight of hemoglobin (MCH) in the red corpuscles. The concentration of hemoglobin in the red cells (MCHC) remains normal. The macrocytic anemias, in general, are of two types, Table 6). The megaloblastic, macrocytic anemias are characterized by the presence of megaloblasts in the bone marrow and are related to a lack of vitamin B_{12}, pteroylglutamic (folic) acid and related substances, as mentioned ear-

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TABLE 6.—CLASSIFICATION OF MACROCYTIC ANEMIAS

DISEASE	PROBABLE PATHOGENESIS
I. Megaloblastic macrocytic anemias*	
A. Conditions responding to purified liver extract, vitamin B_{12} or pteroylglutamic acid	
1. Pernicious anemia†	Lack of gastric ("intrinsic") factor
2. Sprue, idiopathic steatorrhea	Impaired absorption
3. Resection of small intestine	Impaired absorption
4. Nontropical nutritional macrocytic anemia	Dietary deficiency
5. Tropical macrocytic anemia	Dietary deficiency
6. Macrocytic anemia with Diphyllobothrium infestation	Assimilation of vitamin B_{12} by worm, thus depriving host
B. Conditions apparently responding only or most often to pteroylglutamic acid (PGA) rather than vitamin B_{12}	
7. Megaloblastic anemia of infancy	PGA deficiency associated with dietary deficiency of ascorbic acid
8. Megaloblastic anemia of pregnancy	Dietary deficiency? Increased requirements for fetus? Presence of inhibitor or antagonist?
9. "Refractory megaloblastic" anemia	Impaired metabolism of PGA?
10. "Achrestic" anemia	Impaired metabolism of PGA?
II. Nonmegaloblastic macrocytic anemias: Some instances of macrocytosis due to	
1. Acute posthemorrhagic anemia	Presence in blood of many immature erythrocytes
2. Hemolytic anemia	Presence in blood of many immature erythrocytes
3. Aplastic anemia	Unknown
4. Hypothyroidism	Unknown
5. Liver disease	Unknown

*In practice, the most common cause of "macrocytic anemia" is laboratory error, and this is most often due to errors in red corpuscle counting.

†Pernicious anemia is distinguished from the other conditions listed in that achlorhydria is always present and neurologic changes may occur.

lier. To be distinguished from these are the nonmegaloblastic, macrocytic anemias, which do not respond to administration of vitamin B_{12} or folic acid. These include cases of macrocytic anemia associated with hypothyroidism and with liver disease, as well as some cases of aplastic anemia. The nonmegaloblastic, macrocytic anemias also include a number of conditions which ordinarily produce normocytic anemia. The macrocytosis depends on the fact that immature red cells, in general, are larger than their fellow, mature corpuscles. Consequently, in conditions which ordinarily produce normocytic anemia, when there is an accompanying very intense activity of the bone marrow with liberation into the circulation of many immature cells, a temporarily macrocytic anemia develops.

The *normocytic anemias* are those characterized by red cells of normal average size and hemoglobin content. Theoretically and actually, these are due to: (1) the sudden loss of blood; (2) the destruction of blood, acute or chronic; (3) lack of blood formation, or (4) hydremia, in which event there may be no true anemia.

The *simple microcytic anemias*, as already mentioned, are characterized by a reduction in the size of the cells without a significant reduction in their hemoglobin content. This is the least well defined of the morphologic groups of anemia and is found in association with subacute and chronic noninflammatory disease and various chronic inflammatory conditions.

The *hypochromic microcytic anemias* are characterized by a reduction below normal in the average volume of the red cells, together with a marked reduction in the concentration of hemoglobin. With the exceptions of the congenital and hereditary disorder known as thalassemia and a rare condition known as "hereditary sex-linked anemia" (44), the hypochromic microcytic anemias are the consequence of iron deficiency. This deficiency may be the result of a lack of iron in the diet, defective absorption, chronic loss of blood or excessive demands for iron (growth, repeated pregnancies), but it is most often produced by chronic blood loss (gastrointestinal tract, uterus), aggravated by several of the other factors operating in various degrees and combinations. These anemias respond to the administration of iron.

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Needless to say, the classification of anemia on morphologic grounds is no better than the raw data. If the red cell count, on which the mean corpuscular volume is based, is erroneous, the result not only is useless but may be misleading. As already stated, the physician should always examine the *blood smear* himself—a simple procedure requiring very little time which can prevent serious error and reveal much useful information as well.

When the data are accurate, however, they can be most useful. In the case described in Chart B, the discovery of a hypochromic

<div align="center">

Chart B.—A.J., W M M 45 yr.: "Anemia"

</div>

P.I.: Weakness and dizziness began 8 months before; pallor observed; crampy abdominal pain, stools light brown, mixed with blood; physician noted anemia, achlorhydria; B B_{12} and liver.
Weakness persisted, 20 lb. weight loss.

P.E.: Pallor, koilonychia, systolic apical and basal murmurs, oval mass 3×4 cm. right side abdomen.

Blood: Ht 22, MCV 49, MCC 23; WBC 9000, platelets 229,000.

Barium enema: midportion ascending colon narrowed 8 cm.

Conclusion: Carcinoma of colon presenting itself under guise of anemia. The clue was overlooked for 8 months.

microcytic anemia led to a search for blood loss and the discovery of carcinoma in the cecum.

SIGNIFICANCE OF LEUKOCYTES AND PLATELETS IN STUDY OF ANEMIA.—The usefulness of the leukocytic picture and the platelets in the differential diagnosis of the anemias is frequently overlooked. Demonstration of the existence of pancytopenia with reduction of leukocytes, especially neutrophilic leukocytes, and platelets in addition to anemia suggests aleukemic leukemia, aplastic anemia, myelophthisic anemia, some form of "hypersplenism" or one of the deficiency anemias (8). Anemia in the absence of neutropenia or thrombocytopenia makes these conditions unlikely and should lead one to look for other causes of anemia such as chronic renal disease, malignancy, infection or hypothyroidism. The two case histories in Charts C and D illustrate the point.

When hemolytic anemia is suspected, the bile pigments in the plasma, urine and stool must be studied and other procedures may be necessary as well, particularly the three tube presumptive test and the Coombs test. The osmotic fragility test is still a use-

ful procedure, for the shape of the curve of increased fragility in
congenital hemolytic jaundice is unlike that seen in the acquired
forms (8). For the differentiation of the inborn errors of hemo-
globin production, electrophoretic procedures are necessary (45).

The PRESUMPTIVE TEST (46) is performed by placing washed

Chart C.—V.L., W F M 40 yr.: "Aplastic Anemia"

P.I.: 2 years—weakness, malaise, Hgb. 30%.
No improvement following liver, iron, folic acid, B₁₂, 3 pt. blood.
Worked in rubber factory 10 years before: "anemic."
Conclusion: aplastic anemia.

P.E.: Sallow pallor, BP 180/95, fundi grade ii, flame-shaped hemorrhages,
heart enlarged.

Blood: Ht 23, MCV 93, MCC 33; WBC 6700, neutro. 68%; platelets
240,000, B T 5 min., Cl.ret. good, T T negative.

Urine: Sp.G. 1.007-1.011, alb. ++, WBC, casts, BUN 164, PSP 0%.

Conclusion: Anemia due to chronic pyelonephritis and severe renal in-
sufficiency. No pancytopenia. No basis for diagnosis of aplastic anemia.

Chart D.—L.W., W M M 37 yr.: Weakness, Pallor, Bleeding Tendency

P.I.: Anemia discovered 7 months ago: ℞ liver capsules.
Colds, shaking chills and fever, increasing anemia: liver shots, iron,
6 pt. blood, Pentnucleotide—no improvement.
G-I series negative, stools negative for blood, more transfusions and
injections.

P.E.: Pallor, ecchymoses and petechiae, skin, mucous membranes and
fundi; no splenomegaly, adenopathy or sternal tenderness.

Blood: Ht 19, MCV 86, MCC 36; WBC 1650, neutro. 11%; platelets
60,000, B T 35 min., Cl.ret. poor, T T positive.

Impression: Aplastic anemia.

Additional history: 2 years' Mesantoin therapy for epilepsy.

Conclusion: The hematologic findings led to further questioning and dis-
covery of cause of anemia. Cessation of Mesantoin administration
followed by recovery.

red corpuscles from fresh defibrinated blood into each of three
test tubes. The first is incubated for one to two hours at body
temperature, then centrifuged. If hemoglobin is present in the
supernatant serum, the presence of a *warm hemolysin* is suggested.
The second tube is chilled for 20 minutes in cracked ice, then
incubated for one hour and centrifuged. If the result is positive,
the presence of a *cold hemolysin* is indicated. The test tube
should be examined before it has been warmed. If only *cold*

agglutinins are present and no hemolysins, it will be seen that the red corpuscles agglutinate in the cold but fail to hemolyze when the tube is warmed, the clumps disappearing instead. When cold agglutinins are present, one must be careful not to shake the cells too much while they are agglutinated in the cold, since they may hemolyze and give a false cold hemolysin reaction. The blood placed in the third tube is acidified with carbon dioxide. If hemolysis is apparent after incubation for one hour and subsequent centrifugation, *increased acid hemolysis* is suggested. The result of this test is positive in paroxysmal nocturnal hemoglobinuria.

When positive results are obtained in any one of these tubes, the test should be repeated with adequate controls and by the more complete procedures which are available. Thus, if a cold hemolysin appears to be present, the Donath-Landsteiner test should be carried out.

The COOMBS TEST makes possible the demonstration of univalent, erythrocyte-bound antibody. The "direct" Coombs test is carried out simply by mixing the patient's washed red cells with serum from rabbits immunized to human gamma globulin and examining the mixture for agglutination. It serves to demonstrate the presence of "incomplete" antibodies; that is, those which are attached at some points on the surface of the red corpuscles and require a completing substance, such as antihuman globulin, to cause an agglutination reaction to take place. A positive result has been observed in cases of idiopathic acquired hemolytic anemia, in that type of paroxysmal cold hemoglobinuria which is associated with syphilis and in many instances of "symptomatic" hemolytic anemia. The result has been negative in most cases of congenital hemolytic jaundice and is generally negative in sickle cell anemia, in paroxysmal nocturnal hemoglobinuria and in hemolytic anemia due to various physical or chemical agents.

A positive "direct" Coombs reaction is also observed when isoimmunization to known immune bodies has occurred, as in hemolytic disease of the newborn and in sensitization following transfusion. The "indirect" test serves to differentiate such antibodies. In the "indirect" test antihuman globulin serum is mixed with normal group O, Rh-positive, and Rh-negative red corpuscles which have been incubated in the patient's serum. The

resulting reactions are shown in Table 7. If agglutination occurs
with both Rh-positive and Rh-negative cells, Rh antibodies can
be excluded.

In performing the Coombs test it is important that potent
antiserum be used and adequate controls carried out. False nega-
tive results may occur if the red corpuscles have not been washed
sufficiently or may develop from a prozone reaction due to in-

TABLE 7.—THE COOMBS TEST

Antihuman globulin serum is mixed with_____	Direct Patient's RBCs	Indirect normal RBCs & patient's serum	
		Rh+	Rh—
Acquired hemolytic anemia			
with circulating antibodies..................	+	+	+
without circulating antibodies	+	—	—
due to Rh antibodies in Rh+ infant..........	+	+	—
(erythroblastosis fetalis)			
due to physical or chemical agents...........	—	—	—
Congenital hemolytic anemia..................	—	—	—
(hereditary spherocytosis)*			
Sickle cell anemia............................	—	—	—
Paroxysmal nocturnal hemoglobinuria...........	—	—	—
Paroxysmal cold hemoglobinuria...............	+	—	—
(type associated with syphilis)			

*Occasional finding of positive Coombs test in this and in other hemolytic anemias
where test is usually negative is explained by superimposed, frequently transient epi-
sodes of acquired hemolytic anemia.

adequate dilution of the serum. Cold hemagglutinins may cause
a false positive reaction. That other mechanisms, unrelated to
immune reactions, may also produce a positive Coombs reaction
is indicated by the observation that the intravenous administra-
tion of phenylhydrazine in dogs modifies their red corpuscles in
such a way that a positive direct Coombs reaction develops (47).

The detailed elucidation of a case of hemolytic anemia of the
antibody type will often require the use of still other procedures,
but these, in the main, are quite simple. They include the setting
up of agglutination tests at various temperatures and in several
mediums such as isotonic sodium chloride solution and bovine
albumin solution, this being helpful in demonstrating and char-
acterizing the agglutinin; and the treatment of the red corpuscles
with proteolytic enzymes such as papain and trypsin, which

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renders them more susceptible to the demonstration of anti-bodies. For the antibody tests it is necessary in some instances to use the patient's own red corpuscles rather than any available group O red corpuscles, as is often the practice.

THE MANAGEMENT OF ANEMIAS

It is obvious that a prerequisite for the intelligent management of the anemias is accurate differential diagnosis. This necessi-

TABLE 8.—THERAPEUTIC MEASURES FOR THE ANEMIAS

A. Agents which meet a deficiency
    a) vitamin B_{12}—in pernicious anemia and related disorders
    b) folic acid—in certain rare megaloblastic, macrocytic anemias
    c) iron—in iron deficiencies
    and, perhaps less directly,
    d) desiccated thyroid—in anemia of hypothyroidism
    e) ascorbic acid—in anemia of scurvy
B. Agents which relieve or modify the underlying disorder
    a) antibiotics and other measures for treatment of various infections
    b) chemotherapeutic agents in leukemia and Hodgkin's disease
    c) other measures directed at the underlying disorder
C. Agents which decrease extent of blood destruction
    a) cortisone or ACTH in many instances of acquired hemolytic anemia
    b) splenectomy in congenital hemolytic jaundice; less often in acquired hemolytic anemias
D. Measure which may reduce an inhibitory effect
    a) splenectomy
E. Measures which restore blood volume
    a) whole blood transfusion
    b) administration of washed red corpuscles
F. Measures intended to stimulate erythropoiesis
    a) cobalt
    b) cortisone or ACTH (both are of doubtful value)

tates not only an understanding of the pathogenesis of the ane-mias but a sound foundation in clinical medicine in general since, after all, anemia is but a symptom of disease, not a disease in itself. To all of this must be added good common sense. Thus it is impractical to recommend oral therapy in pernicious anemia when one is dealing with a disease which, if properly treated, will not interfere with the normal life span of the patient. The parenteral administration of vitamin B_{12} at intervals of one or

two months is all that is necessary. Again, the frantic and re-
peated transfusions of blood in a patient who has already be-
come adjusted to a reduced level of hemoglobin is often futile
and wasteful, and is not without some risk. It is usually better
to spare his veins and his finances for attempts to discover the
cause of the anemia with a view to treating the anemia speci-
fically; or, failing this, if the condition is one that can only be
treated by transfusion (e.g., aplastic anemia), it is only necessary
to keep his hemoglobin at a level compatible with moderate
though restricted activity. For the person with a disease of long

TABLE 9.—USES OF LIVER EXTRACT OR VITAMIN B_{12}

Indications:
1. Pernicious anemia, to
   a) replenish stores of anti-pernicious anemia factors
   b) provide reserve for maintenance
2. Megaloblastic macrocytic anemia in sprue, nutritional macrolytic
   anemia, etc.
Dose: For relapse: 15 units (1 cc.) liver extract ⎰ daily until good
              30 μg. B_{12} ⎱ response is observed
     For maintenance: 60 units, or 120 μg., respectively, every 45–60
                    days
Route: Intramuscular; oral administration inefficient
Duration of administration: in pernicious anemia and sprue, permanently
No value as "tonic" or in other types of anemias

duration, even if he is well-to-do, the simplest and cheapest form
of therapy is usually the most satisfactory. Only because it is so
often forgotten need one add that the patient must be given
some understanding of his condition if his continuous co-opera-
tion is to be expected.

If these principles are followed, the treatment of anemia, in-
sofar as it is possible today, is quite simple. In contrast to the
number of widely publicized nostrums, the number of useful
therapeutic measures is very small (Table 8). Of those thera-
peutic agents that may be regarded as specific, iron and vitamin
B_{12} or liver extract are the only important ones. The uses of
folic acid are very limited. To this list of specific agents one
might add desiccated thyroid, since this is required to relieve the
anemia of hypothyroidism. Whether or not ascorbic acid should
be classed as a specific therapeutic agent cannot be stated until

we have a better understanding of the pathogenesis of the anemia in scurvy. It will be noted that all of these can be classified as agents which meet a deficiency. Copper and pyridoxine have not been included since neither copper deficiency nor spontaneously occurring pyridoxine deficiency anemia has been observed in man.

The uses of liver extract or vitamin B_{12} may be listed briefly

TABLE 10.—USES OF FOLIC ACID

Indicated in
  "Pernicious" anemia of pregnancy
  Megaloblastic anemia of infancy
  Refractory megaloblastic or "achrestic" anemia
  Some cases of sprue
Contraindicated in pernicious anemia
Dose: 5–20 mg. daily
Route: Oral
Duration of administration:
  "Pernicious" anemia of pregnancy ⎫ Only until complete remission
  Megaloblastic anemia of infancy ⎭ has been obtained

TABLE 11.—USE OF IRON IN TREATMENT OF ANEMIA

Indication: Iron deficiency anemia *only*
Form: Ferrous sulfate or ferrous gluconate, tablets of 0.325 Gm.
Route: *As a rule oral*, 0.325 Gm. t.i.d., with meals
      Intravenous Fe (saccharated oxide) *only* in
         G-I intolerance (ulcerative colitis, pregnancy (?)) and "refractory" iron deficiency anemia *(rare)*
         Intravenous dose: 25–100 mg. daily until total needed has been given
         Total needed (mg.) = normal Hgb − initial Hgb (Gm./100 cc.) ×0.26
Signs of toxicity: Warmth, palpitation, nausea, vomiting, hyperpnea, precordial pressure

(Table 9). The indications for the use of folic acid are few (Table 10). Iron is effective only when there is a true deficiency of iron (Table 11). There is rarely any need for the parenteral administration of iron. Parenteral iron therapy, it should be noted, is not without some danger.

In the management of acquired forms of hemolytic anemia, cortisone and ACTH have, in our experience, been more valuable than splenectomy. In a number of cases these hormones

have been effective where splenectomy had already failed (Fig. 3). Of the two, cortisone is the more practical since it can be taken orally. To relieve the anemia during a stage of relapse, as much as 400 mg. daily may be necessary. In certain patients,
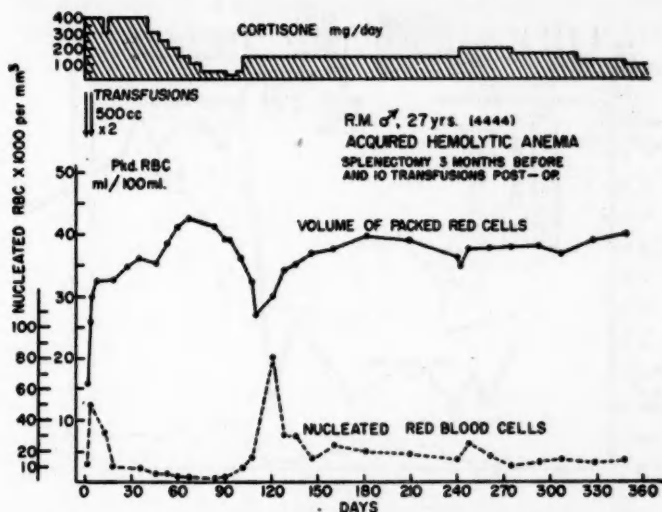

FIG. 3.—Effectiveness of cortisone in a patient (R.M.) with acquired hemolytic anemia (Coombs positive) in whom splenectomy had been of no value. In the three months between operation and treatment shown here, 10 transfusions and smaller doses of cortisone (up to 200 mg.) had been of little value. Relapse occurs when less than 175 mg. cortisone is given each day.

after a time, no more hormone has been required, whereas others relapse unless a maintenance dose of 50–200 mg. daily is furnished.

Insofar as the treatment of anemia is concerned, splenectomy (48), though limited in its role, is sometimes exceedingly helpful. Certainly this is the desirable form of treatment in cases of congenital hemolytic anemia. It is noteworthy that this operation is of no value in hereditary, nonspherocytic hemolytic disease, a

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much rarer disorder (49). In the acquired forms, splenectomy is often disappointing and seems to be less valuable than hormone therapy. However, in certain cases of pancytopenia splenectomy has been the only effective therapeutic agent. This has been true
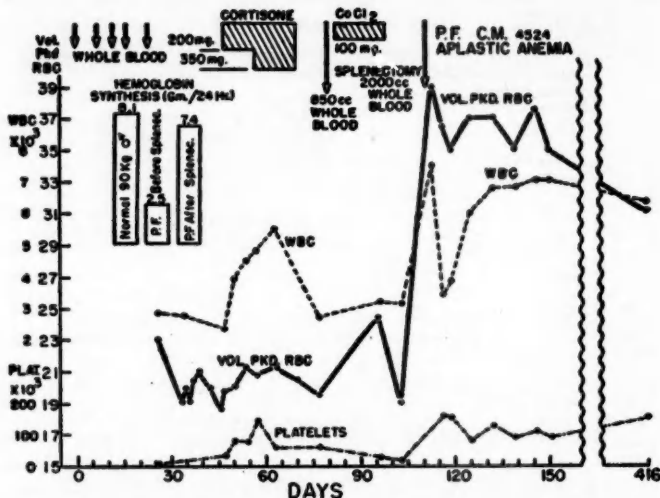

Fig. 4.—Effect of splenectomy in a patient (P.F.) with pancytopenia and bone marrow which was very hypoplastic even when examined by trephine biopsy. Before the studies charted he had received 300 cc. blood transfusions at approximately weekly intervals for 15 months. No significant improvement followed cortisone or cobalt therapy. The improvement after splenectomy has persisted two years. The bone marrow now appears to be more cellular. Hemoglobin synthesis, as measured by iron turnover rate, increased following operation to an almost normal level.

not only in instances of "splenic pancytopenia" where the bone marrow was hyperplastic but also in some cases in which the marrow was hypoplastic (Fig. 4). The improvement which has followed splenectomy would make it seem that by removing this organ one removes the damper which has been holding the metabolic fire at a low level. In such cases the fundamental disorder has not been altered and some anemia has persisted, but

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the new level of hemoglobin has, in several instances, been such that reasonably normal activity could be undertaken.

What is too often overlooked in the management of anemia is the fact that, where the anemia is due to an underlying disorder, the most effective therapeutic agent is that which relieves the underlying condition rather than vitamin B_{12}, iron, folic acid or
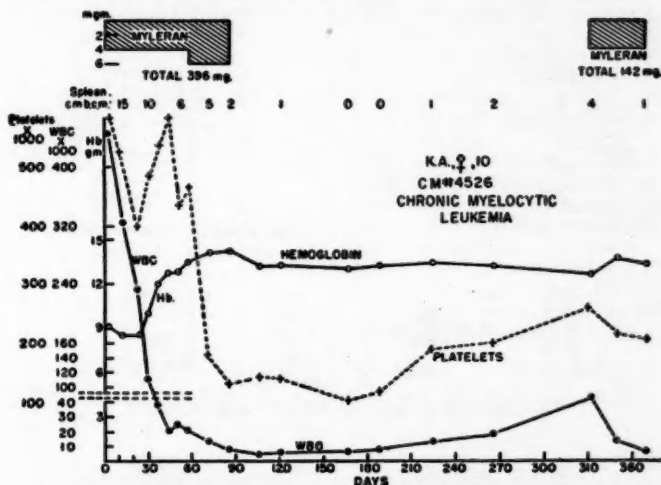

FIG. 5.—Relief of anemia associated with administration of anti-leukemic agent in a case of chronic myelocytic leukemia.

liver extract. The most effective treatment of the anemia associated with infection is treatment of the infection. Likewise, the anemia accompanying leukemia is treated most successfully, even though temporarily, by one of the agents which brings about a remission in that disease (Fig. 5). The role of cobalt in relieving the anemia of infection and that associated with renal disease deserves further study. It has yet to be shown that true benefit results from such therapy.

In conclusion, then, it may be said that the successful treatment of anemia depends on appreciation of the significance of

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anemia and the circumstances under which it may develop, as well as on accurate differential diagnosis. In considering the claims for various proposed therapeutic agents the physician should note the differences, as well as the relation, of experimental studies and clinical practice. In the case of many essential substances, whether vitamins or minerals, human requirements are so low that deficiency is very unlikely or never occurs.
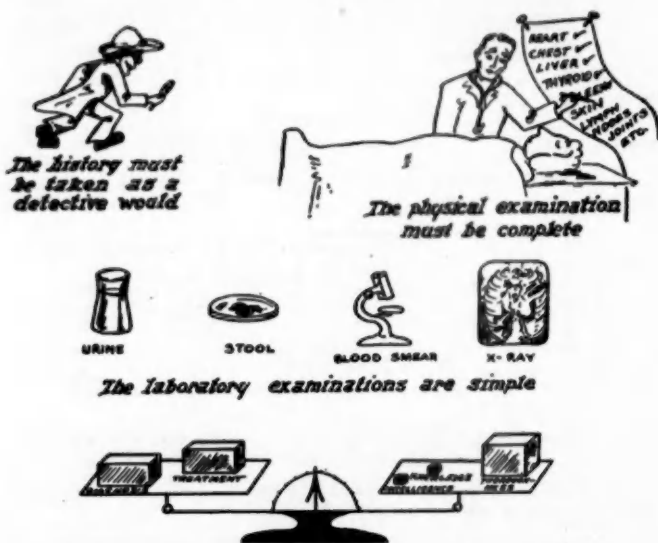

The history must be taken as a detective would

The physical examination must be complete

URINE   STOOL   BLOOD SMEAR   X-RAY

The laboratory examinations are simple

Fig. 6.—Essentials in the diagnosis and treatment of anemia.

In the case of other nutrients, special conditions must exist before deficiency will develop. Storage of essential substances is an important safety factor while synthesis by bacteria growing in the bowel is an occult source of certain vitamins.

The "shotgun" type of hematinic is the modern counterpart of the patent medicine of yesterday. Such treatment is not only useless as a rule; it can be harmful both to the patient's health and to the physician's success (Table 12). There is no short cut to

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the treatment of anemia (50). It is only by the application of the sound principles of good clinical medicine that the great advances of the last few decades can be marshaled for the benefit

TABLE 12.—SHOTGUN THERAPY

ADVANTAGES	DISADVANTAGES
1. No diagnosis required	1. No confirmation of diagnosis by response to specific therapeutic agent
2. Neurasthenics sometimes improve temporarily	2. Underlying factor in pathogenesis of anemia may be overlooked and opportunity for early therapy (e.g., for carcinoma) may be missed
3. Patient ultimately seeks another physician	3. In recommended dosage often does not supply enough of any one substance
	4. Includes many substances not necessary for treatment of patient (copper, molybdenum, cobalt, vitamins such as riboflavin, niacin, pyridoxine, pantothenic acid, etc., etc.)
	5. Cost of treatment multiplied 10- or 20-fold, or more; e.g., $FeSO_4$ 3 cents/day vs. 30–40 cents/day for same agent with euphonious name

of the patient. Good medicine depends on an ounce of knowledge, an equal amount of understanding and a pound of thoroughness (Fig. 6).

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